EXHIBIT 3

EDITORIAL

Use of Powder in the Genital Area and Ovarian Cancer Risk
Examining the Evidence

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Women have used powders for genital hygiene for decades to absorb odor and moisture. While rates of powder use in the genital area have declined over the last 50 years,[1] it remains a routine practice for some women. Commonly used products typically include talc, cornstarch, or some combination of both. Women may apply powders directly to the perineum or onto sanitary napkins, tampons, diaphragms, or underwear. Investigations of an association between the use of talc-containing powders for genital hygiene and epithelial ovarian cancer risks have provided inconsistent results to date and resulted in ongoing controversy. Since 1971, peer-reviewed articles have documented the possible association between talc use and the development of ovarian cancer. However, a PubMed search covering the last 5 decades identified only 17 primary or secondary studies and 36 other articles that were reviews, commentaries, meta-analyses, or letters to the editor.[1-4] In short, while some investigations have been reported, the majority of publications were opinion and discussion articles.

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Several case-control studies identified an increased risk of ovarian cancer with relatively small effect sizes—odds ratios (ORs) of 1.24 to 1.6.[5-8] In a 2018 meta-analysis that included 24 case-control studies and 3 cohort studies, any use of talc in the perineal region was associated with an increased risk of developing epithelial ovarian cancer, with a statistically significant association in case-control studies (OR, 1.35 [95% CI, 1.27-1.43]), and a non-statistically significant association in cohort studies (OR, 1.06 [95% CI, 0.90-1.25]).[2] These studies have been criticized for likely recall bias among patients with cancer, which could increase reported talc use among these patients compared with controls and inflate the calculated association. Cohort studies, such as the Women's Health Initiative (WHI), have not demonstrated the same associations between talc use and ovarian cancer.[9] Since a minority of women in the United States use powder in the genital area, these studies may have lacked power to detect a true association given the relative rarity of epithelial ovarian cancer. Despite this lack of consistency in the primary literature, review articles cited "the robustness of the association between perineal exposure to talc and ovarian cancer."[10-13]

This lack of clarity, as well as recent high-profile litigation regarding the risks of ovarian cancer among users of talc products, prompted O'Brien and colleagues to investigate the question with a larger study population, as reported in this issue of *JAMA*.[14] The authors conducted a pooled analysis of 4 large prospective cohort studies—the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), Women's Health Initiative Observational Study (WHI-OS), and the Sister Study (SIS). Investigators from 3 of these 4 cohort studies had previously published findings regarding talc use and ovarian cancer risk.[9,15,16] The authors pooled data from all 4 studies to create a cohort of more than 252 745 women, of whom 2168 developed ovarian cancer during the study periods. This is the largest reported investigation to date.

Each of the 4 studies used slightly different measures for powder or talc exposure; 3 of the 4 queried women about duration of use (NHSII, SIS, WHI-OS), and 3 of the 4 queried women about frequency of use (NHS, NHSII, SIS). Thus, the authors of the current investigation performed 2 different dose-response analyses with these 2 subgroups of study participants, one for duration and the other for frequency. The authors identified a decrease in use of powder in the genital area over time, with the oldest cohort (the WHI-OS participants) most likely to report use of powder (53%) and younger participants reporting lower rates of use (NHSII, 26% and SIS, 27%).

Given the varying ages of the participants and the varying duration of exposure and follow-up, the investigators calculated an estimated risk of ovarian cancer by the age of 70 in both the exposed and unexposed groups and found a hazard ratio (HR) of 1.08 (95% CI, 0.99-1.17) between ever users and never users of powder in the genital area. This estimate did not reach statistical significance, although it is important to note the CIs. Examination of duration and frequency of powder use in the genital area yielded similar results, with no evidence of a significant dose-response relationship identified in the study population. However, when the analysis was restricted to women with patent reproductive tracts (in situ uterus and fallopian tubes), the HR among ever users of powder was 1.13 (95% CI, 1.01-1.26). For "frequent" use of powder in the genital area vs non-use among women with patent reproductive tracts, the HR was 1.19 (95%CI, 1.03-1.37; *P* value for trend = .03).

The putative etiologic mechanism for talc as a causative agent in epithelial ovarian cancer is via uptake into the vagina, through the cervix and uterus, and through the fallopian tubes into the peritoneal cavity. The evidence of talc in ovarian specimens lends credence to a transgenital transit mechanism.[17-19] Once in contact with the fallopian tubes, ovaries, and peritoneum, it is posited that talc causes local inflammation and triggers a carcinogenic process.[20] Talc has structural similarities to asbestos and is often found in the same mines from which asbestos is obtained. Whether inflammation occurs in response to mineral talc alone or occurs only when talc is contaminated with asbestos remains

an area of controversy. Data regarding rates of asbestos contamination in talc products are scarce and there are public accusations that companies manufacturing talc powder have manipulated or hidden such data.[21,22] Whether the carcinogenic agent is hypothesized to be talc or asbestos, in either case, the agent would need direct access to the fallopian tubes, ovaries, and peritoneum. Thus, the patency of the reproductive tract during the time of exposure is of paramount interest. If a woman has had a hysterectomy or a tubal ligation, then talc applied to the vulva or vagina will have no means of ingress and could not cause inflammation of the fallopian tubes or ovaries.

Given this putative mechanism of exposure, the subgroup analysis of women with patent reproductive tracts is of particular interest. However, it is not possible to equate a patent reproductive tract with exposure and a nonpatent reproductive tract with nonexposure. Women who undergo tubal ligation or hysterectomy (nonpatent) and use powders in the genital area cannot be assumed to have started using them only after their surgeries—in fact, this is highly unlikely as women often begin use of powder in the genital area during adolescence. Thus, the stratification of the groups as patent and nonpatent does not clearly group women into exposed and nonexposed categories. The fact that there are no significant differences in the HRs in the patent (HR, 1.13 [95% CI, 1.01-1.26]) and nonpatent subgroups (HR, 0.99 [95% CI, 0.86-1.15]; *P* value for heterogeneity comparing these subgroups of .15) confirms the overall conclusion that there is no demonstrable statistically significant association between use of powder in the genital area and ovarian cancer risk. This is the key finding of the study. The subgroup analysis suggesting that women with intact reproductive tracts who used powder in the perineal area developed ovarian cancer more frequently than nonusers is below the effect size that epidemiologists generally consider important and should not be selectively highlighted by the statistically unsophisticated reader as evidence of a relationship. In addition, the investigators conducted multiple subgroup analyses increasing the risk of a type I error or a finding that reaches statistical significance but results from chance alone. The fact that this subgroup finding barely achieves statistical significance is further evidence that it is does not represent a true association. The conclusions of the authors, supported by tests of heterogeneity across subgroup HRs, are that there was no evidence of a statistically significant association between use of powder in the genital area and ovarian cancer.

The study by O'Brien et al represents the largest cohort to date to examine whether an association exists between powder use in the genital area and ovarian cancer risk, and the findings are overall reassuring. Yet, despite 3.8 million person-years of observation in the study population, the number of ovarian cancer cases was small, and it is possible that the study was underpowered to detect small increases or decreases in ovarian cancer rates. Future analyses would be strengthened by focusing on women with intact reproductive tracts, with particular attention to timing and duration of exposure to powder in the genital area. Accumulation of such data will take many years, and given the low rates of current powder use among US women, may not be feasible. Nonetheless, the rigorously conducted study by O'Brien et al contributes important and timely data about the potential link between use of powder in the genital area and risk of ovarian cancer.

ARTICLE INFORMATION

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Can an Evidence-Based Approach Improve the Patient-Physician Relationship?

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The importance of the patient-physician relationship has been recognized for millennia.[1,2] Concern that this special relationship is threatened has likely existed nearly as long, although more recently time constraints, insurer demands, novel technologies, and documentation burdens have intensified these worries.[3,4] In their Special Communication in this issue of *JAMA*, Zulman et al report a novel study that proposes a limited number of evidence-based practices that may lead to more meaningful connections between patients and physicians.[5]

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The novelty of this study is the approach the authors used to identify, group, and distill their suggested practices. The authors first performed a literature search that identified 73 studies of evidence-based, interpersonal interventions that could potentially improve practice in 4 domains: patient experience, clinician experience, population health, and health care utilization and cost. Next, a diverse group of physicians, chosen for their exceptional interpersonal skills, were observed in 27 distinct patient encounters. Patients and physicians were debriefed after the interview to identify successful strategies used by the clinicians. Then, nonmedical professionals from 7 professions whose jobs involve intense interpersonal interactions were interviewed to identify cross-disciplinary practices thought to foster human connection.

Through these steps, the research team identified potentially useful clinical approaches that were perceived to contribute to physician "presence," defined by the authors as a purposeful practice of "awareness, focus, and attention with the intent to understand and connect with patients." These practices were rated by patients and clinicians on their likely effects and feasibility in practice. A Delphi process was used to condense 13 preliminary practices into 5 final recommendations, which were (1) prepare with intention, (2) listen intently and completely, (3) agree on what matters most, (4) connect with the patient's story, and (5) explore emotional cues. Each of these practices is complex, and the authors provide detailed explanations, including narrative examples and links to outcomes, that are summarized in the article and included in more detail in the online supplemental material.

If implemented in practice, these 5 practices suggested by Zulman and colleagues are likely to enhance patient-physician relationships, which ideally could help improve physician satisfaction and well-being, reduce physician frustration, improve clinical outcomes, and reduce health care costs. Importantly, the authors also call for system-level interventions to create an environment for the implementation of these practices. Although the patient-physician interaction is at the core of most physicians' activities and has led to an entire genre of literature and television programs, very little is actually known about what makes for an effective relationship. In part, this is because the patient-physician interaction occurs in private, making its study difficult.[6] Efforts to identify effective practices, measure their effectiveness, and learn to teach them are uncommon. The authors' methods of searching for strategies that have some evidentiary support, enhancing their search with clinical experiences and nonclinical expertise, and then synthesizing this information into potentially usable strategies are impressive. They also emphasize the importance of culturally sensitive care and caution against assumptions based on race, ethnicity, gender, socioeconomic status, or past encounters.

However, there are challenges in considering the results of the study. One reason might be the lack of a clear connection between the evidence and the recommendations. A report that focused on motivational interviewing in nursing practice was used to bolster the recommendation to "connect with the patient's story."[7] While the advice to prepare and listen to a patient would be advised by most practicing clinicians without reading this Special Communication, "listen intently and completely" and "explore emotional cues" are such broad and generic recommendations that physicians might as well be advised to be attentive and kind.

The recommendations are on strongest ground in linking the 5 recommended practices to the domains of improved patient and clinician satisfaction. It is less clear if following the recommended practices will actually lead to improved clinical outcomes. For example, in support of the "explore emotional cues" recommendation, Zulman et al cited the "population health" benefit of a study that showed an association between an intervention enhancing clinician empathy and a reduction of common cold symptoms from 7 days to 5.9 days.[8]